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NIH	Fiche to Paper	Journal
TITLE:	CURRENT OPINION IN RHEUMATOLOGY	
PUBLISHER/PLACE:	Lippincott Williams And Wilkins Philadelphia Pa	
VOLUME/ISSUE/PAGES:	1991 Jun;3(3):472-80	472-80
DATE:	1991	
AUTHOR OF ARTICLE:	Wallach S	
TITLE OF ARTICLE:	Paget's disease and fibrous dysplasia.	
ISSN:	1040-8711	
OTHER NOS/LETTERS:	Library reports holding volume or year 9000851 1883702	
SOURCE:	PubMed	
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Paget's disease and fibrous dysplasia

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Many papers were published on both Paget's disease and fibrous dysplasia during the past year. In Paget's disease, evidence for a generalized, probably viral disorder of the skeleton has been adduced, although focal radiologic features dominate the clinical picture. Unusual clinical manifestations were highlighted in several clinical reports. A search for biochemical abnormalities other than increased serum alkaline phosphatase and urinary hydroxyproline levels yielded evidence for secondary hyperparathyroidism in many cases, and also, a confusing array of abnormalities in vitamin D metabolite levels. The application of newer imaging techniques such as computed tomography, MR imaging, bone marrow scintigraphy, and thermography was reported. The year's reports particularly highlighted new forms of effective therapy, including intranasal calcitonin, second- and third-generation bisphosphonates, and gallium nitrate. Finally, the feasibility of joint replacement in arthritic joints secondary to Paget's disease was again documented. Fibrous dysplasia continued to be an enigmatic disorder with no new insights as to etiology. Reports of unusual clinical features, imaging characteristics, bony distribution, and an array of endocrine linkages were prominent. A highlight of the year's reports was the discovery of an increased female sex steroid receptor number on dysplastic cells, and the possibility that sex steroids linked to their receptors may be responsible for the bony overgrowth. Concern was again expressed as to the possibility of malignant transformation of dysplastic lesions and the possible contribution of radiotherapy treatment to sarcoma development.

Current Opinion in Rheumatology 1991, 3:472-480

Paget's disease

Paget's disease, a disease primarily of older individuals, is believed to be a slow virus infection of osteoclasts. After a prolonged latent period, putative viral activation of the infected osteoclasts results in accelerated skeletal turnover with severe bone resorption, followed by equally unregulated, chaotic reparative bone formation. The net result is an enlarged but defective skeleton that is highly vascular and painful, and is subject to deformity, pathologic fractures, and neurologic deficits secondary to the involvement of the skull and vertebral column. With regard to pathogenesis, Kahn [1•] has recently published an editorial proposing that osteoblasts may be the actual site of primary viral infection whereas the osteoclasts represent a permissive environment for secondary viral infection. One of Kahn's key assumptions is that Paget's disease is fundamentally a local disorder. However, a recent study by Kukita *et al.* [2], reviewed earlier [3],

showed that multinucleated cells grown from the marrow from uninvolved sites in Paget's disease patients have the same abnormal ultrastructural and biochemical characteristics as those grown from pagetic sites, thus strongly suggesting that Paget's disease is a generalized rather than a focal disorder. There are other objections to Kahn's proposal, including the absence of viral-like inclusion bodies in pagetic osteoblasts.

Unusual manifestations

Several studies were published describing unusual clinical manifestations of Paget's disease. Fisher [4•] reported on two patients in whom nasal symptoms were prominent and clinical and radiographic evaluation revealed significant involvement of the maxilla and ethmoids with facial deformity, obstruction of the lacrimal ducts with epiphora, loosening or drifting of teeth, and neurologic deficits due to nerve compression, such as facial pain, trigeminal neuralgia, and anosmia. In one

Abbreviation

MR—magnetic resonance.

patient, an osteogenic sarcoma developed, characterized by a grotesque facial appearance and a rapidly fatal course. An earlier study by Bickerstaff *et al.* [5], previously reviewed [3], indicated that antipagetic therapy is capable of some alleviation of facial distortion secondary to Paget's disease when malignancy is not a complication.

Monson *et al.* [6•] reported on a patient in whom an exuberant pagetic lesion of the femur resulted in excessive proliferation of periosteal tissue, producing a localized mass suspected to represent sarcomatous degeneration. They noted that such pseudosarcomas require biopsy and careful pathologic examination to prevent unnecessary mutilative surgery. O'Driscoll and Hastings [7•] described a patient with Paget's disease of the femur that spread to the tibia after arthrodesis of the knee joint. Geil and Staple [8•] reported on Paget's disease of both components of congenitally fused cervical vertebrae. Radiologically, Paget's disease does not usually cross joint spaces, but surgical or congenital continuity allows this to occur. Stull *et al.* [9•] have made a detailed study of Paget's disease of the patella. Olivieri *et al.* [10•] reviewed the coexistence of Paget's disease and ankylosing spondylitis. Finally, Gray *et al.* [11•] warned that interlocking medullary nails inserted into long bones with pagetic fractures may themselves fracture because they conform to the pagetic curvature of the bone.

Biochemical characteristics

Three articles were published relating to biochemical characteristics of Paget's disease in addition to the usual increases in serum alkaline phosphatase and urinary hydroxyproline levels. Siris *et al.* [12••] studied parathyroid hormone levels in 39 patients with widely variable degrees of pagetic activity and noted that approximately 20% had parathyroid hormone levels above normal. Parathyroid hormone levels correlated significantly with increased serum alkaline phosphatase, plasma osteocalcin, and urinary hydroxyproline levels. The authors concluded that increases in parathyroid hormone may occur in the setting of greater calcium demand during periods of increased pagetic new bone formation, and may contribute to the pathophysiology of Paget's disease by driving responsive pagetic osteoclasts to yet higher levels of bone resorption activity.

Taylor *et al.* [13•] measured osteocalcin fragments in urine and were able to utilize a 24-hour urine osteocalcin assay as a substitute for serum alkaline phosphatase and plasma osteocalcin measurements as an indicator of pagetic activity. Urinary osteocalcin levels correlated with serum alkaline phosphatase activity with an r value of +0.91. The use of such an assay would obviate interpretive problems involved in random serum osteocalcin sampling, which is subject to considerable diurnal variation.

Devlin *et al.* [14•] reexamined the question of vitamin D status in Paget's disease and during treatment with calcitonin or etidronate. Foldes *et al.* [15], previously reviewed [3], had found that calcitriol (1,25-dihydroxy-vitamin D) levels were increased in 50% of patients, possibly due to 1-hydroxylase activation by increased parathyroid hormone activity [12••], whereas calcifediol (25-hydroxy-vitamin D) and 24,25-dihydroxy-vitamin D levels were normal. Etidronate treatment caused a decrease in calcifediol levels. In contrast, Devlin *et al.* [14•] noted that untreated pagetic patients had decreased baseline levels of both calcifediol and 24,25-dihydroxy-vitamin D but normal levels of calcitriol. Further, in contradistinction to Siris *et al.* [12••], they found normal parathyroid hormone levels. Etidronate therapy did not correct these abnormalities but caused a further decrease in 24,25-dihydroxy-vitamin D levels, as calcitriol levels increased above normal. Calcitonin treatment had no effect on the 24,25-dihydroxy-vitamin D level but transiently increased calcitriol levels. The significance of these new findings is unclear and their disagreement with the earlier results of Foldes *et al.* [15] further clouds the issue. Devlin *et al.* [14•] point out that neither parathyroid hormone nor serum calcium levels explain these alterations in vitamin D metabolite levels and suggest that further investigations be pursued.

Imaging techniques

Several studies were devoted to imaging techniques in Paget's disease. Kelly *et al.* [16•] reported on magnetic resonance (MR) imaging of the skull involved with the lytic component of Paget's disease, so-called osteoporosis circumscripta. MR imaging demonstrated the lesions clearly and was successful in one patient in uncovering sarcomatous degeneration. Trumble *et al.* [17••] reported a case of Paget's disease of the capitate bone of the wrist, confirmed by biopsy, accompanied by a dramatic decrease in signal intensity of both T₁- and T₂-weighted MR images (Fig. 1). They postulated that signal loss was caused by decreased marrow fat in active Paget's disease, similar to that seen in Gaucher's disease and osteonecrosis.

Rudberg *et al.* [18•] utilized bone marrow scintigraphy, a technique different from conventional bone scanning, in which technetium-labeled albumin colloid is injected and then taken up by the reticuloendothelial system, permitting visualization of the central bone marrow involved in hemopoiesis. Among 20 pagetic lesions, 12 showed increased uptake, including five that were peripheral and should not have had uptake. The authors speculated that peripheral uptake is due to increased blood flow and a stimulation of the reticuloendothelial system by the pagetic process. In four pagetic lesions in central areas, there was decreased uptake, which the authors believed was due to replacement of red marrow by pagetic bone. Finally, four lesions had normal uptake and were not distinguished using

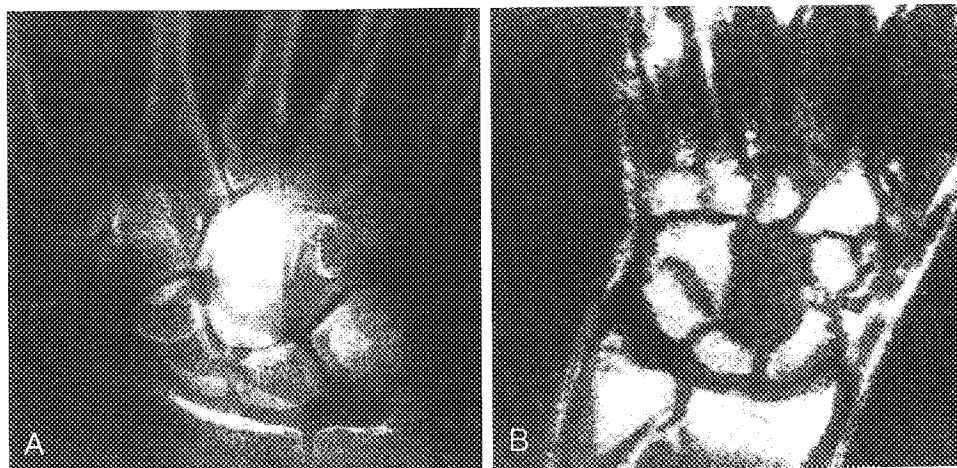


Fig. 1. A, Anteroposterior radiograph of the wrist demonstrating radiodensity of the capitate. B, Coronal MR image of wrist showing corresponding area of signal void. (From Trumble *et al.* [17**]; with permission.)

this methodology. Bone marrow scintigraphy is a useful adjunct to conventional bone scanning in distinguishing pagetic lesions that simulate metastatic disease. Crisp *et al.* [19*] reevaluated thermography in elucidating pagetic lesions and found it to be of some value when the lesions are in superficial bones, such as the tibia. However, pagetic lesions with a great deal of overlying soft tissue, as in the femur, are often missed by thermography.

Treatment

Reginster *et al.* [20], previously reported [3], reaffirmed the value of intranasal salmon calcitonin in treating Paget's disease, even when anti-salmon calcitonin antibodies were present. Muff *et al.* [21**] studied the efficacy of intranasal human calcitonin in pagetic patients whose disease becomes refractory to salmon calcitonin. Some but not all of their patients had binding and neutralizing antibodies to salmon calcitonin. The

patients responded to intranasal human calcitonin with a decrease in the serum alkaline phosphatase level averaging 38% and a decrease in urinary hydroxyproline averaging 20% (Fig. 2). The authors concluded that intranasal human calcitonin offers an alternative to intranasal salmon calcitonin when refractoriness has appeared, similar to the availability of parenteral human calcitonin when resistance to parenteral salmon calcitonin appears.

Nicholas *et al.* [22*] reported on a patient with Paget's disease of the spine with spinal stenosis and radiculopathy in whom etidronate had a beneficial effect on the clinical and radiographic features of the disease, similar to that reported previously with both salmon calcitonin and the bisphosphonates. Stone *et al.* [23*] and O'Doherty *et al.* [24*], like others before them [3], have previously reported biochemical and clinical results using second- and third-generation bisphosphonates intravenously. Both of these stud-

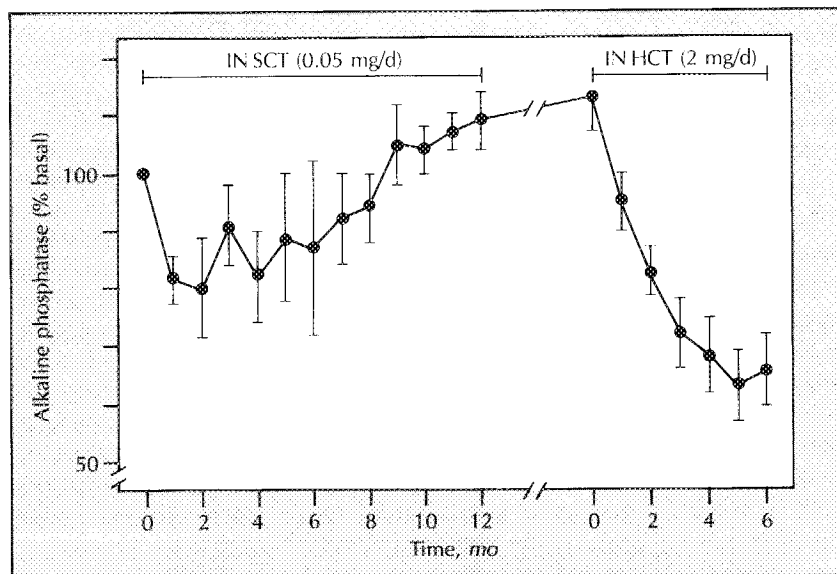


Fig. 2. Mean serum alkaline phosphatase activity, expressed as a percentage of the initial value, during sequential treatment with intranasal salmon calcitonin (IN SCT) and intranasal human calcitonin (IN HCT). The interval between SCT and HCT treatment ranged from 10 to 23 months. (From Muff *et al.* [21**]; with permission.)

ies used low doses in relatively brief treatment programs. In common with the second-generation bisphosphonate disodium pamidronate, O'Doherty *et al.*'s third-generation bisphosphonate, aminohydroxybutyridene bisphosphonate, which is derived from disodium pamidronate, caused a transient decrease in the leukocyte count and short-lived fever in a few patients. In a letter to the editor of *Lancet*, Matkovic *et al.* [25•] replied to previous criticism (also published in *Lancet* and previously reported upon [3]) of their use of gallium nitrate in Paget's disease. Matkovic *et al.* believe that negative comparisons of gallium to aluminum are not justified, and provided additional toxicity data in rats given subcutaneous gallium nitrate in which there was some histotoxicity affecting the lungs and kidneys, but brain histology was normal. As to allegations of using excessive dosage, Matkovic *et al.* pointed out that their doses were similar to those used by their critics. However, they did concede that the ideal dose of gallium nitrate has not yet been established.

Two studies concerned surgical aspects of Paget's disease. Ludkowski and Wilson-MacDonald [26••] reported on a 17-year experience performing 37 total hip arthroplasties in 30 Paget's disease patients. They noted 70% good to excellent results and 30% fair to poor results. In the 11 patients with fair to poor results, the preoperative presence of coxa vara, acetabular protrusion, and femoral bowing were negative prognostic indicators. Intraoperative difficulties were noted in nine patients, consisting of excessive bleeding, hard bone, and difficulty gaining exposure secondary to acetabular protrusion. Nine patients had medical therapy preoperatively with either calcitonin or etidronate, but the doses and their duration, temporal relationship to the surgery, and effects on outcome were not discussed.

Cameron [27•] reported on two patients in whom he performed total knee replacement using noncemented devices. The patients were followed up for 2 years and had good to excellent results. In one patient, the bone of the distal femur was very hard and the femoral component tended to rotate posteriorly on insertion, without influencing the overall result.

Review articles

Finally, three lengthy reviews of Paget's disease were published during the year. Fallon and Schwamm's [28••] review concentrated on the pathology and differential diagnosis of the disease and has excellent illustrative material. Little space was devoted to treatment, however. Cantrill and Anderson's review [29•] unfairly impugned calcitonin therapy and concentrated heavily on disodium pamidronate therapy, probably because of these authors' predominant experience with this agent. Stumpf [30•] reviewed pharmacologic management and provided an excellent discussion of attempts to utilize combinations of various pharmacologic agents to improve the results of treatment. She

concluded that although combination therapy may provide some benefits, it can only be recommended for patients who do not respond to treatment with single agents.

Fibrous dysplasia

Fibrous dysplasia of bone is a disorder of unknown cause characterized by the focal replacement of normal bone with an irregular network of collagenous matrix arranged in a connective tissue stroma characteristic of woven rather than lamellar bone. The bone matrix is immature and poorly mineralized, as well as excessive in amount, and the proliferation of poorly mineralized woven bone gives rise to expansion of the bony confines, distortion, and structural weakness. Grossly, the lesions are rubbery and compressible, grayish white in color with considerable vascularity, and with a gritty texture. Most cases involve a single bone but approximately one third of the cases are of the polyostotic form, usually with an asymmetric or unilateral distribution. Pfeffer *et al.* [31••] reviewed 22 young female patients with the polyostotic form seen at the National Institutes of Health and noted that the most frequently affected areas are the base of the skull, mandible, facial bones, femora, and legs (Fig. 3), whereas the least frequently affected areas are the hands, wrists, ankles, feet, sacrum, and vertebrae. The large majority of their patients also had precocious puberty, approximately two thirds had the characteristic café-au-lait spots, and approximately one third had elevated serum alkaline phosphatase levels. They noted that the serum alkaline phosphatase level often did not correlate with the degree of involvement. All of their cases were sporadic and none had a known hereditary basis. Their most severely affected patients had more than one fracture per year with impaired ambulation, immobilization, and clinically evident skull deformities.

Association with other endocrine abnormalities

The cause of fibrous dysplasia is unknown, but there are such extensive linkages to other endocrine abnormalities that many theories invoke endocrine involvement in its causality. Pensler *et al.* [32••] prepared osteoblast cell cultures from three children with fibrous dysplasia and noted that their osteoblasts had a two- to threefold greater number of estrogen and progesterone receptors, whereas osteoblasts prepared from uninvolved bone had normal receptor levels. Because estrogen and progesterone are postulated to play important roles in the regulation of bone growth and metabolism, the presence of an excess of female sex steroid receptors may be responsible for the localized bony overgrowth characteristic of the condition. This finding is compatible with the known clinical worsening of fibrous dysplasia in many patients during puberty and during pregnancy. Macari *et al.* [33•] re-

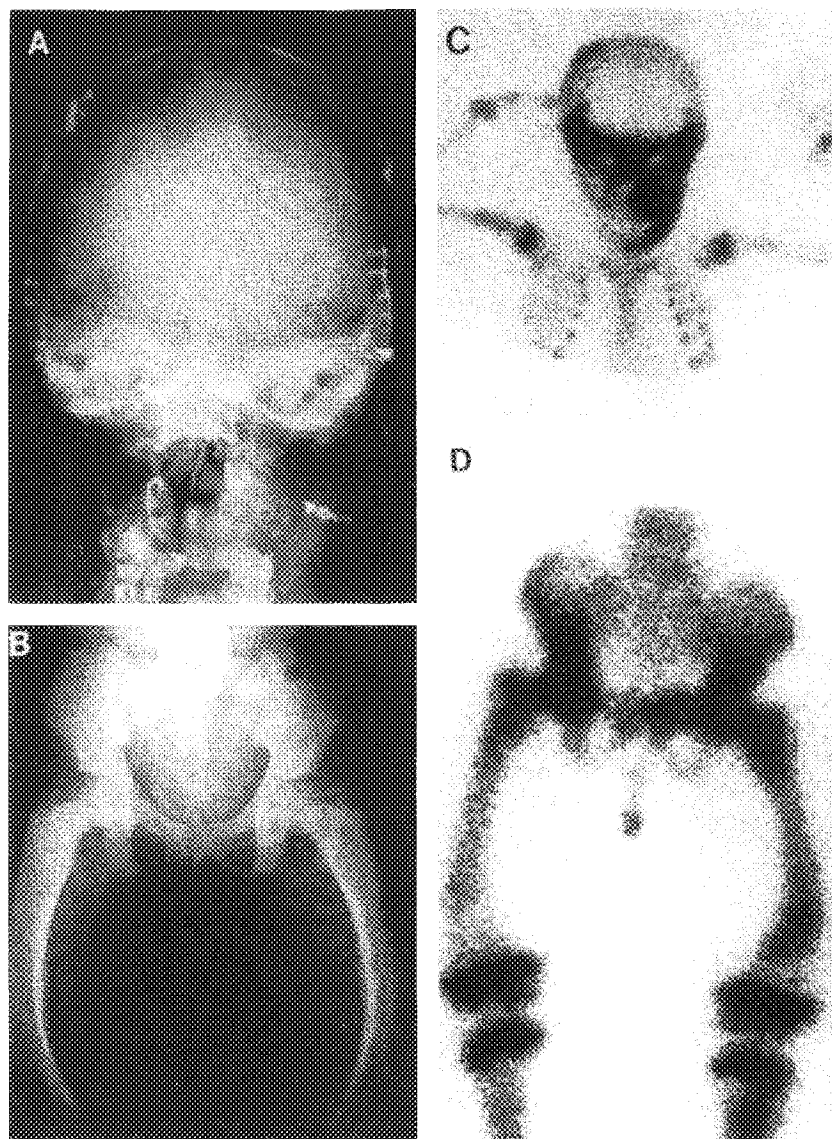


Fig. 3. Widespread fibrous dysplasia as seen on skull (A) and femoral (B) radiographs and corresponding bone scans (C and D). (From Pfeffer *et al.* [31**]; with permission.)

ported on a patient who developed a pathologic fracture during the administration of oral contraceptives. They speculated that the estrogen contained in the birth control pills may have been responsible, and cautioned against the use of oral contraceptives in fibrous dysplasia.

Among the endocrine linkages of fibrous dysplasia, precocious puberty is very common and results from autonomous ovarian activity rather than pituitary influence. On the other hand, acromegaly with increases in both growth hormone and prolactin levels has also been noted in many fibrous dysplasia patients. Some patients have evidence for a pituitary adenoma, such as the cases of Pun *et al.* [34•] and O'Laughlin *et al.* [35•]. However, according to Cuttler *et al.* [36**], although their studies in fibrous dysplasia showed that growth hormone secretion was similar to that seen in patients with pituitary adenomas, there was no evi-

dence of pituitary tumors. They believe there is abnormal hypothalamic regulation or an embryologic defect in pituitary cellular differentiation and function responsible for the hormonal excess. Mortensen *et al.* [37**] reported on two young women with skull involvement and acromegaly who were treated with radiotherapy. After irradiation, one patient developed sarcomatous degeneration of the fibrous dysplasia skull lesion.

Hyperthyroidism is also seen in fibrous dysplasia with some frequency, and Gallacher *et al.* [38•] are of the opinion that it is of autoimmune type. Feuillan *et al.* [39•], in studying the National Institutes of Health group of young women with fibrous dysplasia, noted that none of the patients had hyperthyroidism, but one third had sonographic thyroid abnormalities consisting of generalized inhomogeneity, hypoechoic regions, and echogenic nodule-like regions. In the patients with abnormal ultrasonographic findings, serum thyroid-stim-

ulating hormone levels were suppressed, suggesting that these findings might be the forerunner of later hyperthyroidism. None of their patients had evidence of thyroid-stimulating antibodies. Other endocrinopathies that have been reported in fibrous dysplasia are primary hyperparathyroidism and Cushing's syndrome, but no new cases were reported during the past year.

Imaging findings

Several studies were devoted to imaging findings in fibrous dysplasia. Kransdorf *et al.* [40**] reviewed the Armed Forces Institute of Pathology experience as to the spectrum of radiologic, bone scan, computed tomography, MR imaging, and pathologic features to be expected in this disease. Hardoff *et al.* [41*] reported on a patient in whom bone scintigraphy demonstrated multiple discrete areas of increased radiotechnetium uptake in the ribs and skull that were at first thought to be due to multiple bone metastases. A biopsy of the eighth rib showed fibrous dysplasia instead, and the lesions were unchanged 8 years later. Utz *et al.* [42*] pointed out that typical MR images of fibrous dysplasia lesions show expansion of the involved bones with a reduced T₁ signal and a variable T₂ signal (Fig. 4).

Particular areas of involvement

Three reports were devoted to a consideration of particular areas of involvement. Kreutziger [43*] reviewed jaw involvement and advocated that complete resection be attempted when feasible. Lesser procedures are strictly for short-term palliation and temporary cosmetic improvement. Stompro and Bunkis [44*] reported on a patient with nasal obstruction secondary to craniofacial fibrous dysplasia for whom surgical treatment

was highly successful. On the other hand, Smith *et al.* [45*], in attempting to treat surgically an unusual case in which there was severe cervical spine involvement, reported that the operative procedure resulted in a fatal outcome.

Malignant transformation

The issue of malignant transformation of fibrous dysplasia is of great concern, especially because there is anecdotal evidence that radiotherapy therapy of the lesions, once frequently practiced, may promote sarcomatous degeneration. Chetty *et al.* [46**] reported malignant transformation in three cases, and they believe that fibrous dysplasia is basically a premalignant condition. As noted earlier, Mortensen *et al.* [37**] encountered sarcomatous degeneration of the skull in a woman with fibrous dysplasia and acromegaly who received radiotherapy. In contrast, Simpson *et al.* [47*] noted a case in which extensive cystic expansion of a fibrous dysplasia lesion masqueraded as sarcomatous degeneration. Simpson *et al.* warn against a premature diagnosis of sarcoma without biopsy.

This review of the past year's articles on fibrous dysplasia and the review of Stompro *et al.* [48**] indicate that fibrous dysplasia remains an enigma. Although there are certain superficial similarities with Paget's disease in the pathologic, radiographic, and imaging characteristics, fibrous dysplasia is a far different condition that has been inadequately studied because of its relative rarity. It is exceedingly important to recognize fibrous dysplasia when it presents itself, because both conservative and surgical measures can be taken that may be of benefit.

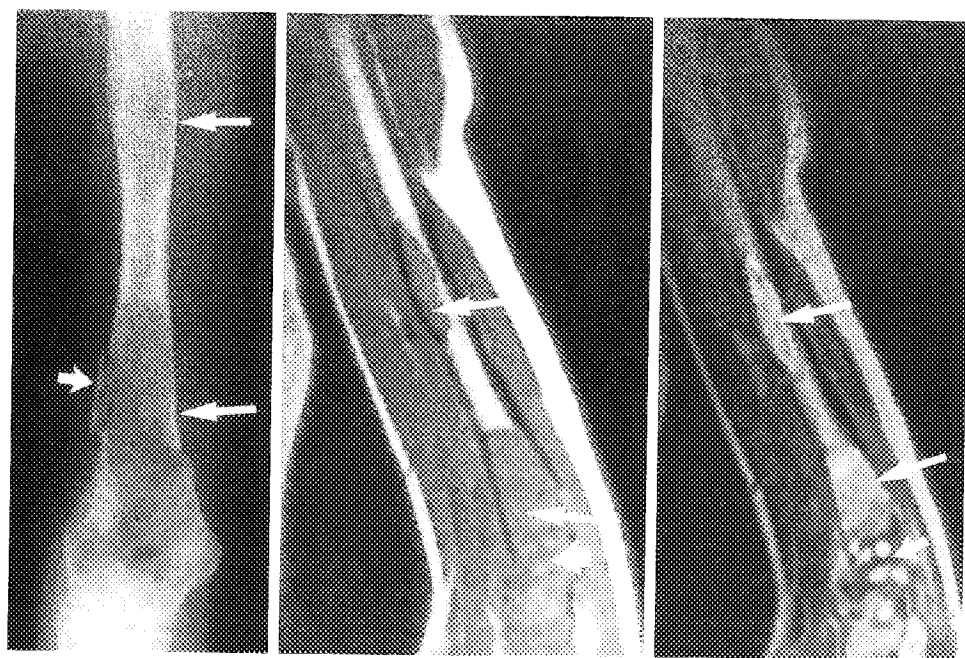


Fig. 4. Fibrous dysplasia of the humerus as imaged by radiography (*left*), coronal T₁-weighted MR scan (*middle*), and T₂-weighted MR scan (*right*). The radiograph shows two sites of fibrous dysplasia (*large arrows*) and a pathologic fracture (*small arrow*). The lesions show a reduced T₁ signal and an intermediate T₂ signal surrounded by a hyperintense rim (*large arrows*). (From Utz *et al.* [42*]; with permission.)

References and recommended reading

Papers of special interest, published within the annual period of review, have been highlighted as:

- Of interest
- Of outstanding interest

1. KAHN AJ: The viral etiology of Paget's disease of bone: a new perspective. *Calcif Tissue Int* 1990, 47:127-129.

Based on unconfirmed assumptions that osteoclast precursors show no evidence of viral infection whereas osteoblasts carry viral RNA, the author proposes a new theory that the viral etiology of Paget's disease is carried by the osteoblast, whereas the osteoclast represents a permissive site of viral assembly.

2. KUKITA A, CHENU C, MCMANUS LM, MUNDY GR, ROODMAN GD: Atypical multinucleated cells form in long-term marrow cultures from patients with Paget's disease. *J Clin Invest* 1990, 85:1280-1286.

3. WALLACH S: Paget's disease and osteogenesis imperfecta. *Curr Opin Orthop* 1990, 2:109-120.

4. FISHER EW: Rhinological manifestations of Paget's disease of bone (osteitis deformans). *J Craniomaxillofac Surg* 1990, 18:169-172.

Clinical and radiographic features of Paget's disease of the maxilla and ethmoids are described in two cases. One patient later developed rapidly fatal sarcomatous degeneration.

5. BICKERSTAFF DR, DOUGLAS DL, BURKE PH, O'DOHERTY DP, KANIS JA: Improvement in the deformity of the face in Paget's disease treated with diphosphonates. *J Bone Joint Surg* 1990, 72B:132-136.

6. MONSON DK, FINN HA, DAWSON PJ, SIMON MA: Pseudosarcoma in Paget's disease of bone. *J Bone Joint Surg* 1989, 71A:453-455.

The authors point out that exuberant pagetic lesions can be confused with sarcomatous degeneration and that careful examination of biopsy specimens can obviate unnecessary surgery.

7. O'DRISCOLL SW, HASTINGS DE: Extension of monostotic Paget's disease from the femur to the tibia after arthrodesis of the knee. *J Bone Joint Surg* 1989, 71A:129-132.

In a pagetic patient in whom a knee arthrodesis was performed for uncontrollable pain secondary to osteoarthritis, Paget's disease was observed to spread from the femur to the tibia.

8. GEIL GE, STAPLE TW: Case report 595. *Skeletal Radiol* 1990, 19:290-293.

Paget's disease of both components of congenitally fused vertebrae can occur. Continuity of the marrow spaces bearing the cell types active in skeletal turnover is undoubtedly responsible for these observations.

9. STULL MA, MOSER RP JR, VINH TN, KRANSDORF MJ, CALLAGHAN JJ: Paget's disease of the patella. *Skeletal Radiol* 1990, 19:407-410.

Paget's disease of the patella can vary radiologically from minimal trabecular coarsening in a patella of near normal size to extensive cortical thickening in a greatly enlarged patella.

10. OLIVIERI I, SEMERIA R, GEMIGNANI G, TAVONI A, ALOISI D, GIUSTARINI S: Coexisting ankylosing spondylitis and Paget's disease. *Clin Rheum* 1990, 9:235-238.

The authors add a 16th case of coexisting Paget's disease and ankylosing spondylitis (HLA-B27 negative in this case) to the literature. However, there is no apparent etiologic connection between the two conditions.

11. GRAY RES, HALL MA, ANSELL BM, JENKINS EA, SWANN M: Problem fracture in Paget's disease of bone. *J R Soc Med* 1989, 82:626-627.

Intramedullary nails inserted across fractures in deformed pagetic bones may be subject to fracture if there is poor fracture healing or progressive deformity of the involved bone.

12. SIRIS ES, CLEMENS TP, MCMAHON D, GORDON A, JACOBS TP, CANFIELD RE: Parathyroid function in Paget's disease of bone. *J Bone Miner Res* 1989, 4:75-79.

Secondary hyperparathyroidism may occur in Paget's disease and drive pagetic osteoblasts to yet higher levels of bone resorption activity.

13. TAYLOR AK, LINKHART S, MOHAN S, CHRISTENSON RA, SINGER FR, BAYLINK DJ: Multiple osteocalcin fragments in human urine and serum as detected by a mid-molecule osteocalcin radioimmunoassay. *J Clin Endocrinol Metab* 1990, 70:467-472.

Twenty-four-hour urinary osteocalcin assays are as reliable as serum alkaline phosphatase measurements as an indicator of pagetic activity, and more reliable than plasma osteocalcin assays because the latter undergo diurnal variation, lessening the reliability of random sampling.

14. DEVLIN RD, GUTTERIDGE DH, PRINCE RL, RETALLACK RW, WORTH GK: Alterations in vitamin D metabolites during treatment of Paget's disease of bone with calcitonin or etidronate. *J Bone Miner Res* 1990, 5:1121-1126.

A variety of confusing changes in vitamin D metabolite activity occur basally, and during treatment of Paget's disease. Further investigation is warranted.

15. FOLDES J, SHAMIR S, KIDRONI G, MENCZEL J: Vitamin D in Paget's disease of bone. *Clin Orthop Rel Res* 1989, 243:275-279.

16. KELLY JK, DENIER JE, WILNER HI, LAZO A, METES JJ: MR imaging of lytic changes in Paget's disease of the calvarium. *J Comput Assist Tomogr* 1989, 13:27-29.

MR imaging is particularly successful in demonstrating the lytic component of Paget's disease of the skull and can uncover rare cases of sarcomatous degeneration.

17. TRUMBLE TE, WU RK, RUWE PA: Paget's disease in the hand: correlation of magnetic resonance imaging with histology. *J Hand Surg* 1990, 15A:504-506.

A pagetic lesion of a carpal bone was confusing from the radiographic point of view. MR changes consisting of reduced T₁ and T₂ signals may permit more definitive diagnosis in such cases.

18. RUDBERG U, AHLBACK SO, UDEN R: Bone marrow scintigraphy in Paget's disease of bone. *Acta Radiol* 1990, 31:141-144.

Bone marrow scintigraphy, which is different from conventional bone scanning, may help distinguish confusing pagetic lesions from bone metastases.

19. CRISP AJ, SMITH ML, SKINGLE SJ, SMITH M, PAGE THOMAS DP, HAZLEMAN BL: The localization of bone lesions of Paget's disease by radiographs, scintigraphy and thermography: pain may be related to bone blood flow. *Br J Rheum* 1989, 28:266-268.

Thermography may elucidate pagetic lesions in superficial bones, but often fails when there is a great deal of overlying soft tissue.

20. REGINSTER JY, GENNARI C, MAUTALEN C, DEROISY R, DENIS D, LECART MP, VANDALEM JL, COLLETTE J, FRANCHIMONT P: Influence of specific anti-salmon calcitonin antibodies on biological effectiveness of nasal salmon calcitonin in Paget's disease of bone. *Scand J Rheum* 1990, 19:83-86.

21. MUFF R, DAMBACHER MA, PERRENOUD A, SIMON C, FISCHER JA: Efficacy of intranasal human calcitonin in patients with Paget's disease refractory to salmon calcitonin. *Am J Med* 1990, 89:181-184.

Intranasal human calcitonin offers an alternative to intranasal salmon calcitonin when refractoriness to salmon calcitonin has appeared.

22. NICHOLAS JJ, HELFRICH DJ, COOPERSTEIN L, GOODMAN M: **Clinical and radiographic improvement of bone of the second lumbar vertebra in Paget's disease following therapy with etidronate disodium [case report].** *Arthritis Rheum* 1989, 32:776-779.
Etidronate, like salmon calcitonin and other bisphosphonates, may favorably affect Paget's disease of the spine causing spinal stenosis.
23. STONE MD, HAWTHORNE AB, KERR D, WEBSTER G, HOSKING DJ: **Treatment of Paget's disease with intermittent low-dose infusions of disodium pamidronate (APD).** *J Bone Miner Res* 1990, 5:1231-1235.
Low doses of intravenous disodium pamidronate in a relatively brief treatment program can yield beneficial results in many cases of Paget's disease.
24. O'DOHERTY DP, BICKERSTAFF DR, MCCLOSKEY EV, HAMDY NAT, BENETON MNC, HARRIS S, MIAN M, KANIS JA: **Treatment of Paget's disease of bone with aminohydroxybutylidene bisphosphonate.** *J Bone Miner Res* 1990, 5:483-491.
This bisphosphonate, which is derived from disodium pamidronate, has effects similar to those of disodium pamidronate.
25. MATKOVIC V, APSELOFF G, SHEPARD D, GERBER N: **Hazards of gallium for Paget's disease of bone.** *Lancet* 1990, 335:1099.
Toxicity data in rats do not support concern that gallium may manifest toxicity similar to aluminum when used in high doses in Paget's disease.
26. LUDKOWSKI P, WILSON-MACDONALD J: **Total arthroplasty in Paget's disease of the hip.** *Clin Orthop Rel Res* 1990, 225:160-167.
Total hip arthroplasty can be expected to be highly successful in 70% of Paget's disease cases. Fair to poor results can be predicted if coxa vara, acetabular protrusion, or femoral bowing are present.
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General review of this rare and enigmatic condition.

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